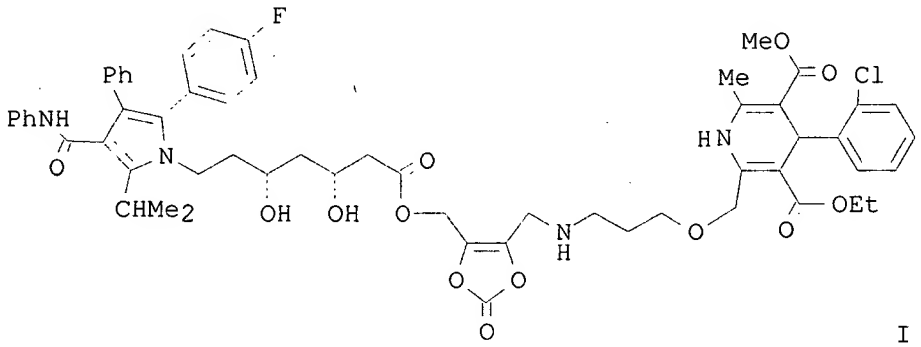
```
=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 14:50:52 ON 28 MAR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.

FILE COVERS 1967 - 28 Mar 2001  VOL 134 ISS 14
FILE LAST UPDATED: 27 Mar 2001  (20010327/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 This file supports REGlstRY for direct browsing and searching of
 all substance data from the REGISTRY file.  Enter HELP FIRST for
 more information.

Now you can extend your author, patent assignee, patent information,
and title searches back to 1907.  The records from 1907-1966 now have
this searchable data in CAOLD.  You now have electronic access to all
of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.


=>

=>

=> d stat quel9

'STAT' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'
'QUEL9' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'
ENTER DISPLAY FORMAT (BIB):end


=> d stat que l9

L1             4 SEA FILE=REGISTRY ABB=ON  PLU=ON  (ATORV/BI OR ATORVASTAT/BI
                 OR ATORVASTATIN/BI)
L2             6 SEA FILE=REGISTRY ABB=ON  PLU=ON  AMLODIPINE/BI
L3               SEL  PLU=ON  L1 1- CHEM :      13 TERMS
L4           383 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L5           383 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR ?ATORVASTAT?
L6               SEL  PLU=ON  L2 1- CHEM :      29 TERMS
L7          1010 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L8          1010 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 OR ?AMLODI?
L9             6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND L8


=> d ibib abs hitrn 19 1-6


L9   ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:861673  HCAPLUS
DOCUMENT NUMBER:          134:29248
TITLE:                    Preparation and uses of mutual prodrugs of
                        amlodipine and atorvastatin
INVENTOR(S):              Chang, George; Hamanaka, Ernest Seiichi; Lamattina,
                          John Lawrence
PATENT ASSIGNEE(S):       Pfizer Products Inc., USA
SOURCE:                   PCT Int. Appl., 33 pp.
```

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

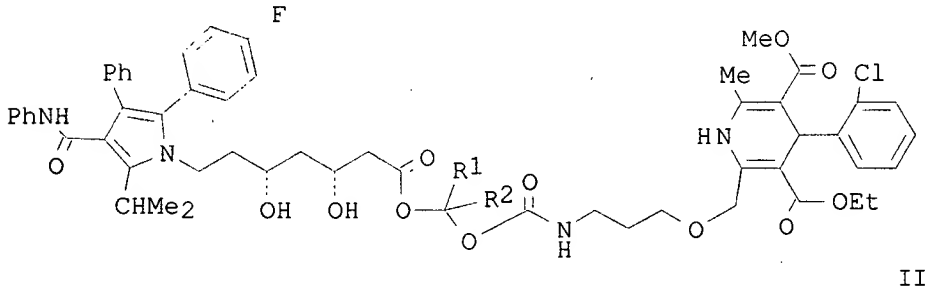
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073298	A1	20001207	WO 2000-IB313	20000320

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-136608 19990527
OTHER SOURCE(S): MARPAT 134:29248
GI



I



II

AB This invention relates to mutual prodrugs of **amlodipine** and **atorvastatin**, e.g. I and II (R1 = R2 = H; R1, R2 = H, C1-4-alkyl), and to pharmaceutical compns. thereof. Thus, II (R1 = R2 = H) was prepd. via reaction of **amlodipine** with ClCO2CH2Cl in CHCl3 contg. pyridine followed by reaction with **atorvastatin calcium** salt in DMF. This invention also relates to methods of treating angina pectoris, atherosclerosis, and hypertension and hyperlipidemia in a mammal using those prodrugs and compns. and to methods of managing cardiac risk in a mammal, including humans, presenting with symptoms of cardiac risk by administering those prodrugs and compns.

IT **88150-42-9, Amlodipine 103129-81-3, (R)-Amlodipine 103129-82-4, (S)-Amlodipine 134523-00-5, Atorvastatin**

RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and uses mutual of prodrugs of **amlodipine** and **atorvastatin**)

IT **88150-42-9DP, Amlodipine**, mutual prodrugs with **atorvastatin 134523-00-5DP, Atorvastatin**, mutual prodrugs with **amlodipine**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and uses mutual of prodrugs of **amlodipine** and **atorvastatin**)

IT **111470-99-6, Amlodipine besylate**
134523-03-8, Atorvastatin calcium
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and uses mutual of prodrugs of **amlodipine** and **atorvastatin**)

REFERENCE COUNT: 1
REFERENCE(S): (1) Pfizer; WO 9911259 A 1999 HCAPLUS

L9 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:861653 HCAPLUS
DOCUMENT NUMBER: 134:21483
TITLE: Mutual salt of **amlodipine** and **atorvastatin**
INVENTOR(S): Chang, George; Hamanaka, Ernest Seiichi
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073271	A1	20001207	WO 2000-IB590	20000508

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-136269 19990527

AB This invention relates to a mutual salt of **amlodipine** and **atorvastatin**, pharmaceutical compns. and methods of treating angina pectoris, atherosclerosis and combined hypertension and hyperlipidemia in mammals with such a mutual salt. This invention also relates to methods of managing cardiac risk in a mammal presenting with symptoms of cardiac risk, including humans by administering such a mutual salt and compns. Thus, a free acid of **atorvastatin** in EtOAc soln. was added to the free base of **racemic amlodipine** to give the diastereomeric salt of the 2 drugs.

IT **134523-03-8, Atorvastatin hemicalcium**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mutual salt of **amlodipine** and **atorvastatin**)

IT **88150-42-9, Amlodipine 111470-99-6, Amlodipine besylate 134523-00-5, Atorvastatin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mutual salt of **amlodipine** and **atorvastatin**)

REFERENCE COUNT: 1
REFERENCE(S): (1) Buch, J; WO 9911259 A 1999 HCAPLUS

L9 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:772453 HCAPLUS
DOCUMENT NUMBER: 133:305601
TITLE: Synergistic antioxidant effects of **amlodipine** and **atorvastatin**, and therapeutic use in cardiovascular disease
INVENTOR(S): Mason, R. Preston
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064443	A1	20001102	WO 2000-US10465	20000418

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1999-130665 19990423
US 1999-145305 19990723
US 1999-151121 19990827
US 1999-166592 19991119

AB The combination of **amlodipine** with either **atorvastatin** or **atorvastatin** metabolite shows a synergistic antioxidant effect on lipid peroxidn. in human low-d. lipoproteins and membrane vesicles enriched with polyunsatd. fatty acids. Inhibition of oxy-radical damage by this drug combination was obsd. at therapeutic levels in a manner that could not be reproduced by the combination of **amlodipine** with other statins or the natural antioxidant, vitamin E. The basis for this potent activity is attributed to the chem. structures of these compds. and their mol. interactions with phospholipid mols., as detd. by x-ray diffraction analyses. This combination therapy can be used to treat cardiovascular disorders, esp. coronary artery disease, by increasing the resistance of low-d. lipoproteins and vascular cell membranes against oxidative modification.

IT **88150-42-9, Amlodipine 214217-86-4, o-Hydroxyatorvastatin**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic antioxidant effects of **amlodipine** and **atorvastatin**, and therapeutic use in cardiovascular disease)

IT **88150-42-9D, Amlodipine**, derivs. **111470-99-6, Amlodipine besylate 134523-00-5, Atorvastatin 134523-00-5D, Atorvastatin**, derivs. and hydroxylated metabolites **134523-03-8, Atorvastatin calcium**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic antioxidant effects of **amlodipine** and **atorvastatin**, and therapeutic use in cardiovascular disease)

REFERENCE COUNT: 1
REFERENCE(S): (1) Pfizer Inc; WO 9911259 A1 1999 HCAPLUS

L9 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:725436 HCAPLUS
DOCUMENT NUMBER: 133:301171
TITLE: Compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents
INVENTOR(S): Chen, Feng-jing; Patel, Manesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059475	A1	20001012	WO 2000-US7342	20000316

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-287043 19990406

AB The present invention is directed to a pharmaceutical compn. including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of prepg. such compns. by providing a compn. of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compns. of the invention are particularly suitable for use in oral dosage forms. A carrier contg. concd. phosphoric acid 0.025, Tween-20 0.3, Arlacel 186 0.2, sodium taurocholate 0.15, propylene glycol 0.3 g was formulated. Itraconazole was included in the carrier at 30 mg/mL for testing the stability of the itraconazole soln. upon diln. in simulated gastric fluid.

IT **88150-42-9, Amlodipine 134523-00-5, Atorvastatin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. hydrophobic therapeutic agents and carriers contg. ionizing agents and surfactants and triglycerides)

REFERENCE COUNT: 3
REFERENCE(S):
(1) Blair; US 4306981 A 1981 HCAPLUS
(2) Hauer; US 5342625 A 1994 HCAPLUS
(3) Story; US 4944949 A 1990 HCAPLUS

L9 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:608551 HCAPLUS
DOCUMENT NUMBER: 133:213151
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000050007 A1 20000831 WO 2000-US165 20000105
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-258654 19990226

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the surfactants contg. the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical compn. contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.

IT **88150-42-9, Amlodipine 134523-00-5, Atorvastatin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)

REFERENCE COUNT: 4
REFERENCE(S):
(1) Crooks; US 4572915 A 1986 HCAPLUS
(2) Muller; US 4719239 A 1988 HCAPLUS
(3) Schmidt; US 4727109 A 1988 HCAPLUS
(4) Story; US 4944949 A 1990 HCAPLUS

L9 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:184129 HCAPLUS
DOCUMENT NUMBER: 130:205138
TITLE: Therapeutic combinations comprising **amlodipine** and **atorvastatin**
INVENTOR(S): Buch, Jan; Scott, Robert Andrew Donald
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911259	A1	19990311	WO 1998-IB1225	19980811
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9885548	A1	19990322	AU 1998-85548	19980811
EP 1003503	A1	20000531	EP 1998-936587	19980811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9812030	A	20000926	BR 1998-12030	19980811
NO 2000000998	A	20000228	NO 2000-998	20000228
PRIORITY APPLN. INFO.:			US 1997-57275	19970829
			WO 1998-IB1225	19980811

AB This invention relates to pharmaceutical combinations of

amlodipine or a pharmaceutically acceptable acid addn. salt thereof and **atorvastatin** or a pharmaceutically acceptable salt thereof, kits contg. such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of **amlodipine** and **atorvastatin** whereby those synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and those subjects presenting with symptoms of cardiac risk, including humans.

IT **88150-42-9, Amlodipine 111470-99-6, Amlodipine besylate 134523-00-5, Atorvastatin 134523-03-8, Atorvastatin calcium**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive and antihyperlipidemic compns. contg. **amlodipine** and **atorvastatin**)

REFERENCE COUNT: 2
REFERENCE(S):
(1) Jukema, J; Arteriosclerosis Thrombosis and Vascular Biology 1996, V16(3), P425 HCAPLUS
(2) Orekhov, A; Cardiovascular Drugs and Therapy 1997, V11(2), P350

=>

=>

=> fil reg

FILE 'REGISTRY' ENTERED AT 14:52:48 ON 28 MAR 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 American Chemical Society (ACS)

STRUCTURE FILE UPDATES: 27 MAR 2001 HIGHEST RN 329180-43-0
DICTIONARY FILE UPDATES: 27 MAR 2001 HIGHEST RN 329180-43-0

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=>

=>
=>

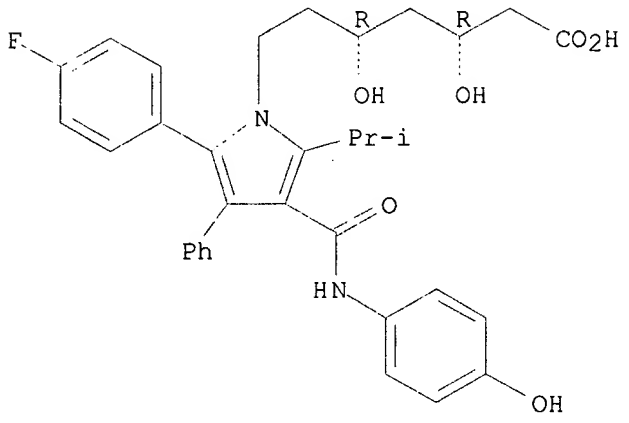
=>

=> d ide can l1 1-4

L1 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN 214217-88-6 REGISTRY
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-[[(4-hydroxyphenyl)amino]carbonyl]-5-(1-methylethyl)-3-phenyl-, (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **p-Hydroxyatorvastatin**
FS STEREOSEARCH

MF C33 H35 F N2 O6
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



9 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
10 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:50965

REFERENCE 2: 131:252054

REFERENCE 3: 131:164924

REFERENCE 4: 131:709

REFERENCE 5: 130:191350

REFERENCE 6: 130:32629

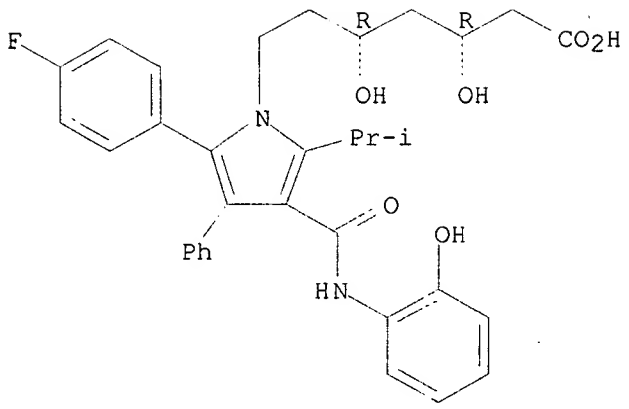
REFERENCE 7: 130:32628

REFERENCE 8: 129:285845

REFERENCE 9: 129:285588

L1 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN 214217-86-4 REGISTRY
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-4-[[(2-hydroxyphenyl)amino]carbonyl]-5-(1-methylethyl)-3-phenyl-, (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **o-Hydroxyatorvastatin**
FS STEREOSEARCH
MF C33 H35 F N2 O6
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXLIT

Absolute stereochemistry.



11 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:50965

REFERENCE 2: 133:305601

REFERENCE 3: 131:346095

REFERENCE 4: 131:252054

REFERENCE 5: 131:164924

REFERENCE 6: 131:709

REFERENCE 7: 130:191350

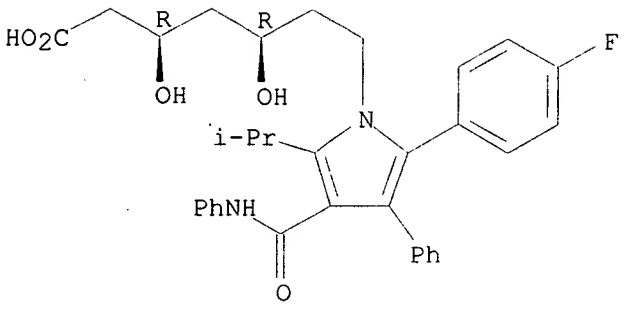
REFERENCE 8: 130:32629

REFERENCE 9: 130:32628

REFERENCE 10: 129:285845

L1 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN 134523-03-8 REGISTRY
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), (.beta.R,.delta.R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), [R-(R*,R*)]-
OTHER NAMES:
CN **Atorvastatin calcium**
CN **Atorvastatin hemicalcium**
CN CI 981
CN Lipitor
CN YM 548
FS STEREOSEARCH
MF C33 H35 F N2 O5 . 1/2 Ca
SR CA
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, DDFU, DIOGENES, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
CRN (134523-00-5)

Absolute stereochemistry.



● 1/2 Ca

45 REFERENCES IN FILE CA (1967 TO DATE)
45 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:95065

REFERENCE 2: 134:29248

REFERENCE 3: 134:21483

REFERENCE 4: 134:21435

REFERENCE 5: 133:344417

REFERENCE 6: 133:305601

REFERENCE 7: 133:275803

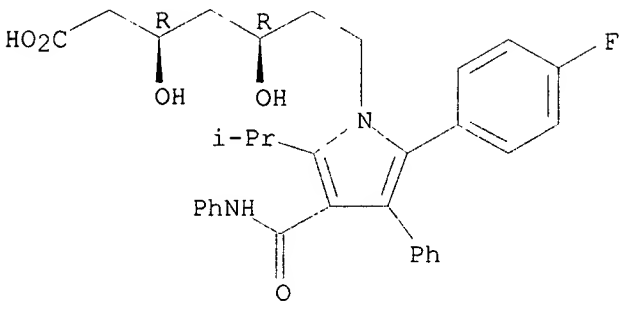
REFERENCE 8: 133:48894

REFERENCE 9: 132:308162

REFERENCE 10: 131:267055

L1 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2001 ACS
RN 134523-00-5 REGISTRY
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (.beta.R,.delta.R)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, [R-(R*,R*)]-
OTHER NAMES:
CN (.beta.R,.delta.R)-2-(p-Fluorophenyl)-.beta.,.delta.-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid
CN **Atorvastatin**
FS STEREOSEARCH
MF C33 H35 F N2 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CEN, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IMSDIRECTORY, IPA, MRCK*, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



277 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
281 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:198100

REFERENCE 2: 134:178396

REFERENCE 3: 134:173058

REFERENCE 4: 134:173034

REFERENCE 5: 134:168357

REFERENCE 6: 134:157413

REFERENCE 7: 134:141522

REFERENCE 8: 134:125794

REFERENCE 9: 134:125790

REFERENCE 10: 134:125381

=>

=>

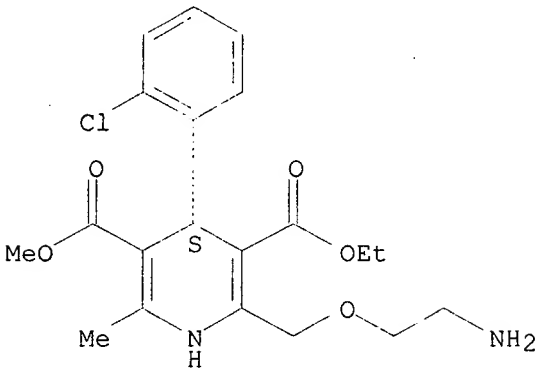
=> d ide can l2 1-6

L2 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN 150566-71-5 REGISTRY
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (-)-, monobenzenesulfonate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(-)-Amlodipine besylate**
FS STEREOSEARCH
MF C20 H25 Cl N2 O5 . C6 H6 O3 S
SR CA
LC STN Files: CA, CAPLUS, DRUGPAT, DRUGUPDATES, TOXLIT, USPATFULL

CM 1

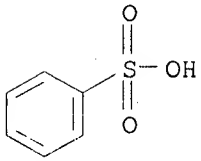
CRN 103129-82-4
CMF C20 H25 Cl N2 O5

Absolute stereochemistry.



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



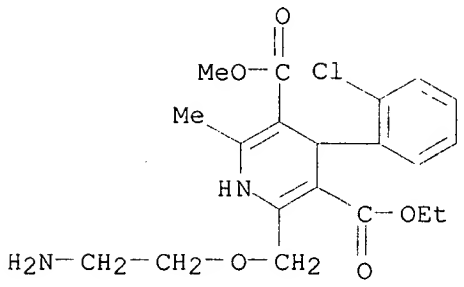
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:188578

L2 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN 111470-99-6 REGISTRY
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzenesulfonic acid, compd. with 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate (1:1)
OTHER NAMES:
CN (.+-.)-3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate
CN **Amlodipine benzenesulfonate**
CN **Amlodipine besylate**
CN Istin
CN Norvasc
CN UK 48340-26
DR 115633-24-4, 156366-25-5
MF C20 H25 Cl N2 O5 . C6 H6 O3 S
CI COM
SR CAS Registry Services
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DIOGENES, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IMSDIRECTORY, IPA, MRCK*, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

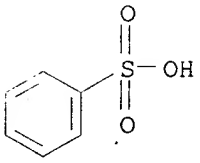
CM 1

CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 98-11-3
CMF C6 H6 O3 S



75 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
76 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:152752

REFERENCE 2: 134:121057

REFERENCE 3: 134:121035

REFERENCE 4: 134:100763

REFERENCE 5: 134:46898

REFERENCE 6: 134:37028

REFERENCE 7: 134:32972

REFERENCE 8: 134:29248

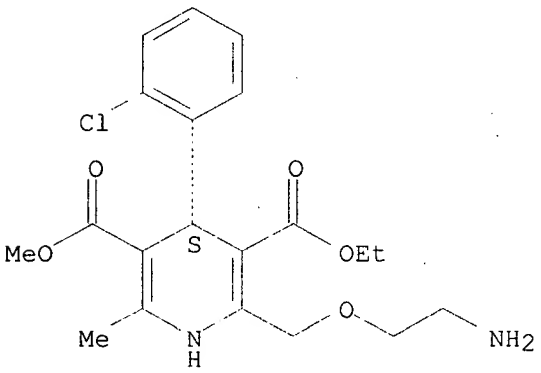
REFERENCE 9: 134:21483

REFERENCE 10: 133:305601

L2 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN 103129-82-4 REGISTRY
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (S)-
OTHER NAMES:
CN **(-)-Amlodipine**

CN **(S)-(-)-Amlodipine**
CN **(S)-Amlodipine**
CN **l-Amlodipine**
FS STEREOSEARCH
DR 150566-70-4
MF C20 H25 Cl N2 O5
CI COM
SR CA
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, CA, CAPLUS, CEN, DRUGPAT, DRUGUPDATES, PHAR, PROMT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



28 REFERENCES IN FILE CA (1967 TO DATE)
28 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:121039

REFERENCE 2: 134:29248

REFERENCE 3: 132:26949

REFERENCE 4: 131:219237

REFERENCE 5: 130:124968

REFERENCE 6: 130:104763

REFERENCE 7: 128:262037

REFERENCE 8: 128:175767

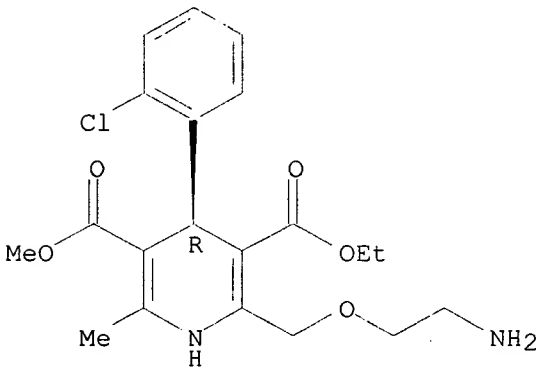
REFERENCE 9: 127:351317

REFERENCE 10: 127:103850

L2 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN 103129-81-3 REGISTRY
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (4R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (R)-
OTHER NAMES:
CN **(+)-Amlodipine**
CN **(R)-(+)-Amlodipine**
CN **(R)-Amlodipine**

CN **d-Amlodipine**
FS STEREOSEARCH
MF C20 H25 Cl N2 O5
CI COM
SR CA
LC STN Files: ANABSTR, BEILSTEIN*, CA, CAPLUS, DRUGPAT, PROMT, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



27 REFERENCES IN FILE CA (1967 TO DATE)
27 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:121039

REFERENCE 2: 134:29248

REFERENCE 3: 132:180209

REFERENCE 4: 132:26949

REFERENCE 5: 131:219237

REFERENCE 6: 130:124968

REFERENCE 7: 130:104763

REFERENCE 8: 128:262037

REFERENCE 9: 128:175767

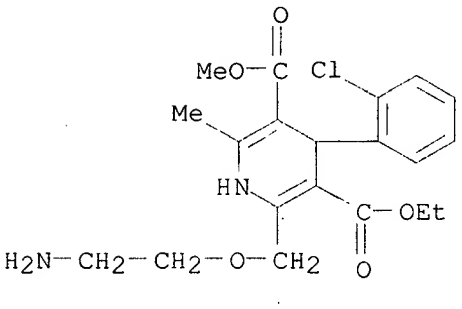
REFERENCE 10: 127:351317

L2 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN 88150-47-4 REGISTRY
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (Z)-2-butenedioate (1:1)
OTHER NAMES:
CN **Amlodipine maleate**
FS STEREOSEARCH
DR 135877-50-8
MF C20 H25 Cl N2 O5 . C4 H4 O4
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMCATS, DRUGPAT, IPA,

MRCK*, PHAR, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

CM 1

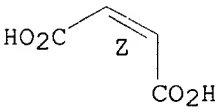
CRN 88150-42-9
CMF C20 H25 Cl N2 O5



CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.



13 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:172829

REFERENCE 2: 131:18930

REFERENCE 3: 131:5189

REFERENCE 4: 128:262037

REFERENCE 5: 126:207339

REFERENCE 6: 124:106098

REFERENCE 7: 120:38145

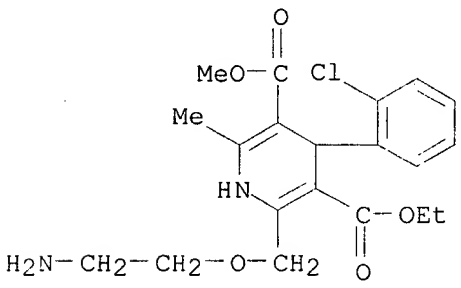
REFERENCE 8: 115:64374

REFERENCE 9: 112:30245

REFERENCE 10: 111:89763

L2 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN 88150-42-9 REGISTRY
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Amlodipine**

CN **Racemic Amlodipine**
FS 3D CONCORD
DR 103069-18-7
MF C20 H25 Cl N2 O5
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, DDFU, DRUGPAT, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



716 REFERENCES IN FILE CA (1967 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
721 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:198104

REFERENCE 2: 134:188205

REFERENCE 3: 134:187688

REFERENCE 4: 134:183470

REFERENCE 5: 134:157360

REFERENCE 6: 134:136711

REFERENCE 7: 134:125732

REFERENCE 8: 134:121039

REFERENCE 9: 134:110304

REFERENCE 10: 134:110298

=> d l4 ibib kwic 32-33

L4 ANSWER 32 OF 37 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1995001096 PCTFULL
TITLE (ENGLISH): PHARMACEUTICAL COMPOSITIONS AND USE THEREOF FOR TREATMENT OF NEUROLOGICAL DISEASES AND ETIOLOGICALLY RELATED SYMPTOMOLOGY
TITLE (FRENCH): COMPOSITIONS PHARMACEUTIQUES ET LEUR UTILISATION POUR LE TRAITEMENT D'AFFECTIONS NEUROLOGIQUES ET DE SYMPTOMOLOGIES A ETIOLOGIES ASSOCIEES
INVENTOR(S): SHAPIRO, Howard, K.
PATENT ASSIGNEE(S): SHAPIRO, Howard, K.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9501096	A1	19950112
DESIGNATED STATES:	AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1994-US7277		19940628
PRIORITY (ORIGINAL):	US 1993-8/062201		19930629

102(b) date

DETD . . . angiotensin converting enzyme inhibitors such as captopril, epi-captopril and zofenopril, which also have free radical scavenging properties (Westlin and Mullane, 1988) ; (e) anti-**hyperlipidemia** agents such assfibric acid derivatives, including gemfibrozil (Lopid) (Garg and Grundy, 1990), bezafibrate (Olsson and Lang, 1978a; Olsson and Lang, 1978b; Zimmermann and. . .

. . .

early atherosclerotic lesions (Steinbrecher, 1987). Use of the invention of US patent application 08/026,617 in combination with previously recognized medicaments for treatment of atherosclerosis, **hypertension** and ischemic heart disease, as defined herein, may provide additional clinical benefit for patients suffering from these chronic, age-related diseases.

. . .

Stern and Haffner, 1991) and prostaglandin 1 oligomers (PGBd (Moss and coworkers, 1978; Polis and Cope, 1980). Previously known medicaments for treatment of **hypertension** (Woodley and Whelan, 1992, pp. 64-75) include diuretics, P-adrenergic antagonists, calcium antagonists, angiotensin converting enzyme inhibitors, centrally acting a-adrenergic agonists, direct-acting vaso-dilators, a-adrenergic. . . antagonists and peripherally acting anti-adrenergic agents. At least one peptide-based renin inhibitor (A-725517, Abbott Laboratories) has also been mentioned as a prospective anti-**hypertensive** agent (Kleinert and coworkers, 1992). Previously known medicaments for treatment of ischemic heart disease include nitroglycerin, P-adrenergic antagonists, calcium channel antagonists and aspirin. . .

. . .

dosage range from 6 mg daily to 120 mg

daily;
isradipine (DynaCirc) , dosage range from 0. 5 mg daily to 20 mg daily;
amlodipine (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to 10 mg daily; and
felodipine (Plendil, Merck & Co.), dosage range. . .
. . .
dosage range from 1 mg daily to 300 mg daily;
and
zofenoprilat, dosage range from 1 mg daily to 150 mg daily;
Q anti-**hyperlipidemia** agents such as
fibric acid derivatives including
gemfibrozil (Lopid, Parke-Davis) , dosage range from 100 mg daily to 1.2 gm daily;
clofibrate (Atromid-E, Wyeth-Ayerst),. . .
. . .
mg daily to 250 mg daily; and
rentiapril, dosage range from 1 mg daily to 150 mg daily;
(b) fibric acid derivative anti-**hyperlipidemia** agents such as
gemfibrozil (Lopid, Parke-Davis), dosage range from 100 mg daily to 1.2 gm daily;
clofibrate (Atromid-a, Wyeth-Ayerst Laboratories), dosage range from 20. . . polymeric 15-keto
prostaglandin B or PGBd , intravenous, intramuscular or subcutaneous dosage range from 5 mg/kg daily to 40 mg/kg daily;
(j) anti-**hypertensive** agents including
oral diuretics such as
bendroflumethiazide (Naturetin) , cdosage range from 0.5 mg daily to 5 mg daily;
benzthiazide (Exna) , dosage range. . .
. . .
(Cardene), dosage range from 6 mg daily to 120 mg daily;
isradipine (DynaCirc) , dosage range from 0.5 mg daily to 20 mg daily;
amlodipine (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to 10 mg daily;
felodipine (Plendil, Merck & Co.), dosage range from. . .
. . .
(Cardene), dosage range from 6 mg daily to 120 mg daily;
isradipine (Dynacirc) , dosage range from 0.5 mg daily to 20 mg daily;
amlodipine (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to A mg daily; and
felodipine (Plendil; Merck & Co.), dosage range. . .
. . .
York, Plenum Press, 1990) pp. 475-484
Nagaoka, A et a!. "Inhibitory effect of idebenone (CV-2619), a novel compound, on vascular lesions in **hypertensive** rats''
Japan. J. Pharmacol. 36:291-299 (1984)
Niemegeers, CJ and Janssen, PA "A systemic study of the pharmacological activities of dopamine antagonists" Life. . .

A preliminary note on a multicenter investigation bearing on 393 subjects with pure or mixed forms of **hyperlipidemia**" Arzneim.- Forsch./Drug Res. 26:906-909 (1976)
Wurtman, RJ gt. 1. "Choline metabolism in cholinergic neurons:

CLM . . . drug is a calcium channel antagonist; an IV angiotensin converting enzyme inhibitor; a P-adrenergic antagonist; an antihypertensive drug; an a-adrenergic agonist; an anti-**hyperlipidemia** fibric acid derivative; a nitrate drug; or an antiarrhythmic drug.

L4 ANSWER 33 OF 37 USPATFULL
ACCESSION NUMBER: 97:83944 USPATFULL
TITLE: Methods of treating neurological diseases and etiologically related symptomology using carbonyl trapping agents in combination with previously known medicaments
INVENTOR(S): Shapiro, Howard K., 214 Price Ave. F32, Narberth, PA, United States 19072

	NUMBER	DATE
PATENT INFORMATION:	US 5668117	19970916
APPLICATION INFO.:	~~US 1993-62201~~	19930629 (8)

102(e)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-26617, filed on 23 Feb 1993, now abandoned which is a continuation of Ser. No. US 1991-660561, filed on 22 Feb 1991, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: Leary, Louise
LEGAL REPRESENTATIVE: Perrella, D. J.
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
LINE COUNT: 3963
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . miotine and derivatives therof (Moos and Hershenson, 1989); (g) calcium channel blocker agents such as diltiazem, verapamil, nifedipine, nicardipine, isradipine, **amlodipine** and felodipine; (h) biogenic amines and agents related thereto (Moos and Hershenson, 1989) such as clonidine, a noradrenergic alpha.sub.2 -receptor. . .
SUMM . . . enzyme inhibitors such as captopril, epi-captopril and zofenopril, which also have free radical scavenging properties (Westlin and Mullane, 1988); (e) anti-**hyperlipidemia** agents such as fibric acid derivatives, including gemfibrozil (Lopid) (Garg and Grundy, 1990), bezafibrate (Olsson and Lang, 1978a; Olsson and. . .
SUMM . . . application Ser. No. 08/026,617, filed Feb. 23, 1993, now abandoned, in combination with previously recognized medicaments for treatment of atherosclerosis, **hypertension** and ischemic heart disease, as defined herein, may provide additional clinical benefit for patients suffering from these chronic, age-related diseases.. . . 1991) and prostaglandin B.sub.1 oligomers (PGB.sub.x) (Moss and coworkers, 1978; Polis and Cope, 1980). Previously known medicaments for treatment of **hypertension** (Woodley and Whelan, 1992, pp. 64-75) include diuretics, beta-adrenergic antagonists, calcium antagonists, angiotensin-converting enzyme inhibitors, centrally acting alpha-adrenergic agonists, direct-acting. . . peripherally acting anti-adrenergic agents. At least one peptide-based renin inhibitor

(A-725517, Abbott Laboratories) has also been mentioned as a prospective anti-**hypertensive** agent (Kleinert and coworkers, 1992). Previously known medicaments for treatment of ischemic heart disease include nitroglycerin, beta-adrenergic antagonists, calcium channel. . .

DETD **amlodipine** (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to 10 mg daily; and

DETD (d) anti-**hyperlipidemia** agents such as

DETD (b) fibric acid derivative anti-**hyperlipidemia** agents such as

DETD (j) anti-**hypertensive** agents including

DETD **amlodipine** (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to 10 mg daily;

DETD **amlodipine** (Norvasc, Pfizer Labs Division), dosage range from 0.5 mg daily to 10 mg daily; and

DETD Nagaoka, A. et al. "Inhibitory effect of idebenone (CV-2619), a novel compound, on vascular lesions in **hypertensive** rats" Japan. J. Pharmacol. 36:291-299 (1984)

DETD . . . 178 in man. A preliminary note on a multicenter investigation bearing on 393 subjects with pure or mixed forms of **hyperlipidemia**" Arzneim.-Forsch./Drug Res. 26:906-909 (1976)

L1 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011263 PCTFULL
TITLE (ENGLISH): COMBINATION THERAPY COMPRISING AMLODIPINE AND A STATIN COMPOUND
TITLE (FRENCH): THERAPIE COMBINEE COMPRENANT DE L'AMLODIPINE ET UN COMPOSE DE STATINE
INVENTOR(S): **BUCH, Jan**; SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S): PFIZER PRODUCTS INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9911263	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-IB1220 19980810
PRIORITY (ORIGINAL): US 1997-60/057555 19970829

L1 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011259 PCTFULL
TITLE (ENGLISH): THERAPEUTIC COMBINATIONS COMPRISING AMLODIPIN AND ATORVASTATIN
TITLE (FRENCH): COMBINAISONS THERAPEUTIQUES COMPRENANT DE L'AMLODIPINE ET DE L'ATORVASTATINE
INVENTOR(S): **BUCH, Jan**; SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S): PFIZER INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9911259	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-IB1225 19980811
PRIORITY (ORIGINAL): US 1997-60/057275 19970829

=> d l7 ibib kwic 550-555

L7 ANSWER 550 OF 963 MEDLINE
ACCESSION NUMBER: 96113507 MEDLINE
DOCUMENT NUMBER: 96113507
TITLE: **Lipid-lowering** activity of **atorvastatin** and lovastatin in rodent species: triglyceride-lowering in rats correlates with efficacy in LDL animal models.
AUTHOR: Krause B R; Newton R S
CORPORATE SOURCE: Department of Atherosclerosis Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner Lambert Company, Ann Arbor, MI 48105, USA.
SOURCE: ATHEROSCLEROSIS, (1995 Oct) 117 (2) 237-44.
Journal code: 95X. ISSN: 0021-9150.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
TI **Lipid-lowering** activity of **atorvastatin** and lovastatin in rodent species: triglyceride-lowering in rats correlates with efficacy in LDL animal models.
AB Since inhibitors of HMG-CoA reductase **lower** plasma triglycerides rather than **cholesterol** in rats, we compared the triglyceride-lowering activity of lovastatin in rats to that of **atorvastatin**, a more potent synthetic inhibitor, prior to evaluating these drugs in established animal models in which low density lipoproteins (LDL) rather than high density lipoproteins (HDL) are the major transporters of plasma cholesterol. **Atorvastatin** was more efficacious than lovastatin in normal, chow-fed rats, and more potent in rats with endogenous hypertriglyceridemia (sucrose-fed). In hypertriglyceridemic rats plasma apoB concentrations decreased only with **atorvastatin** (30 mg/kg), and VLDL-triglyceride secretion (Triton method) was also decreased more by **atorvastatin**. The inactive enantiomer of **atorvastatin** did not lower plasma triglycerides. Thus, triglyceride-lowering was dependent upon inhibition of HMG-CoA **reductase**. Liver unesterified **cholesterol** and **cholesteryl** esters (mg/g) were increased by both drugs in normal rats but remained unchanged in hypertriglyceridemic rats. In normal, chow-fed guinea pigs **atorvastatin** was a more potent **cholesterol-lowering** drug, and unlike lovastatin, **lowered** plasma triglycerides and VLDL-**cholesterol**. In casein-fed rabbits with endogenous hypercholesterolemia and in chow-fed rabbits **atorvastatin lowered** LDL-**cholesterol** more potently than lovastatin, but in chow-fed rabbits neither drug had an effect on the in vivo rate of VLDL-lipid. . . conclude that normal rats can be used as a preclinical tool to assess the efficacy of HMG-CoA reductase inhibitors since triglyceride-**lowering** correlates with **cholesterol-lowering** in LDL animal models. In this regard **atorvastatin** is a more potent **hypolipidemic** agent than lovastatin in animals. A common but not sole mechanism for these drugs may be direct inhibition of the. . .

L7 ANSWER 551 OF 963 MEDLINE
ACCESSION NUMBER: 95390983 MEDLINE

DOCUMENT NUMBER: 95390983
TITLE: Comparative effects of HMG-CoA reductase inhibitors on apo B production in the casein-fed rabbit: atorvastatin versus lovastatin.
AUTHOR: Auerbach B J; Krause B R; Bisgaier C L; Newton R S
CORPORATE SOURCE: Department of Atherosclerosis Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, USA..
SOURCE: ATHEROSCLEROSIS, (1995 Jun) 115 (2) 173-80.
Journal code: 95X. ISSN: 0021-9150.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
AB . . . and decreased LDL receptor activity. Pre-established EH in this model was used to assess the ability and mechanism by which **atorvastatin lowers** total plasma **cholesterol** (TPC) compared to the reference agent lovastatin. Rabbits were fed a casein diet for 6 weeks, obtaining average TPC levels. . . into treatment groups based on the 6-week TPC levels, and fed the casein diet alone or in combination with either **atorvastatin** or lovastatin for an additional 6 weeks. Under these conditions, new steady-state cholesterol values were established. Lipoprotein concentrations and distributions were determined at this point. Compared to pretreatment values, TPC were similar in untreated animals. **Atorvastatin,** however, significantly reduced TPC by 38%, 45%, and 54% at the 1, 3, and 10 mg/kg doses, respectively. Statistically significant. . . lowering of TPC (35%) by lovastatin was only achieved at the 10 mg/kg dose. To determine the mechanism by which **atorvastatin** lowered TPC in the EH rabbits, kinetic studies using human [125I]-LDL were performed in a subset of animals maintained on the casein diet alone (n = 5), or those treated with 3 mg/kg of **atorvastatin** (n = 5) or lovastatin (n = 7). In this set of studies, **atorvastatin** significantly lowered TPC compared to control and lovastatin-treated rabbits by 57% and 46%, respectively. Lovastatin treatment resulted in a 20%. . .

L7 ANSWER 552 OF 963 MEDLINE
ACCESSION NUMBER: 95347515 MEDLINE
DOCUMENT NUMBER: 95347515
TITLE: Prospects for drug therapy for hyperlipoproteinaemia.
AUTHOR: Davignon J
CORPORATE SOURCE: Institut de Recherches, Cliniques de Montreal, QC, Canada.
SOURCE: DIABETE ET METABOLISME, (1995 Apr) 21 (2) 139-46. Ref: 58
Journal code: E4J. ISSN: 0338-1684.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
AB . . . the plasma lipid transport system. Promising advances are revealed in both directions. A new synthetic inhibitor of HMG CoA reductase, **atorvastatin,** lowers plasma low-density lipoprotein (LDL)-cholesterol and triglycerides and increases high-density lipoprotein

(HDL)-cholesterol with greater potency than currently available drugs of this class. A highly selective thyromimetic, CGS 26214, virtually devoid of cardiovascular effects, has potent **cholesterol-lowering** activity in several models, reduces post-prandial response to a fat load in rats and markedly lowers Lp(a) concentrations in monkeys. There is a trend to develop **inhibitors** of acyl CoA: **cholesterol** acyltransferase (ACAT) with more than one desirable activity. Thus, ACA-147, which **inhibits cholesterol** absorption, **reduces** LDL, prevents their oxidation and increases HDL-cholesterol, was antiatherogenic in cholesterol-fed rabbits. Sch48461 has emerged as an **inhibitor** of **cholesterol** absorption by an as yet unknown mechanism unrelated to ACAT inhibition, while a synthetic saponin, CP- 148,623, which prevents the. . .

L7 ANSWER 553 OF 963 MEDLINE

ACCESSION NUMBER: 95269007 MEDLINE
DOCUMENT NUMBER: 95269007
TITLE: **Reduction** of LDL **cholesterol** by 25% to 60% in patients with primary hypercholesterolemia by **atorvastatin**, a new HMG-CoA reductase inhibitor.
AUTHOR: Nawrocki J W; Weiss S R; Davidson M H; Sprecher D L; Schwartz S L; Lupien P J; Jones P H; Haber H E; Black D M
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co, Ann Arbor, MI 48105, USA..
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1995 May) 15 (5) 678-82.
Journal code: B89. ISSN: 1079-5642.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508

103

TI **Reduction** of LDL **cholesterol** by 25% to 60% in patients with primary hypercholesterolemia by **atorvastatin**, a new HMG-CoA reductase inhibitor.

AB This 6-week, double-blind clinical trial evaluated lipid parameter responses to different dosages of **atorvastatin** in patients with primary hypercholesterolemia. **Atorvastatin** is a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor under development. After completing an 8-week placebo-baseline dietary phase, 81 patients were randomly assigned to receive either placebo or 2.5, 5, 10, 20, 40, or 80 mg **atorvastatin** once daily for 6 weeks. Plasma LDL **cholesterol reductions** from baseline were dose related, with 25% to 61% reduction from the minimum dose to the maximum dose of 80 mg **atorvastatin** once a day. Plasma total **cholesterol** and apo B **reductions** were also dose related. Previously, **reductions** in LDL **cholesterol** of the magnitude observed in this study have been seen only with combination drug therapy. In this study, **atorvastatin** was well tolerated by **hyperlipidemic** patients, had an acceptable safety profile, and provided greater **reduction** in **cholesterol** than other previously reported HMG-CoA reductase inhibitors.

L7 ANSWER 554 OF 963 MEDLINE

ACCESSION NUMBER: 95142838 MEDLINE
DOCUMENT NUMBER: 95142838
TITLE: Antiatherosclerotic activity of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase in cholesterol-fed rabbits: a biochemical and morphological evaluation.
AUTHOR: Bocan T M; Mazur M J; Mueller S B; Brown E Q; Sliskovic D R; O'Brien P M; Creswell M W; Lee H; Uhlendorf P D; Roth B D; et al
CORPORATE SOURCE: Department of Atherosclerosis Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105..
SOURCE: ATHEROSCLEROSIS, (1994 Nov) 111 (1) 127-42.
Journal code: 95X. ISSN: 0021-9150.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
AB . . . inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which have previously been shown to possess varying degrees of hepatoselectivity in rats. **Atorvastatin**, previously known as CI-981 (2.5 mg/kg), PD135022 (1.0 mg/kg), simvastatin (2.5 mg/kg), lovastatin (2.5 mg/kg), PD134965 (1.0 mg/kg), pravastatin (2.5. . . (2.5 mg/kg) were added to a 0.5% cholesterol, 3% peanut, 3% coconut oil diet and fed for 8 weeks. Although **reductions** in plasma total **cholesterol** of 27% to 60%, VLDL-cholesterol of 31% to 71% and plasma total cholesterol exposure of 37% to 43% were obtained,. . . between these parameters and vascular lipid content, lesion size or monocyte-macrophage content was noted. Iliac-femoral lipid content was unchanged; however, **atorvastatin** and simvastatin significantly **reduced** the **cholesterol** content of the thoracic aorta by 45%-62%. **Atorvastatin** and PD135022 reduced the size of the iliac-femoral lesion by 67% and monocyte-macrophage content by 72%. Simvastatin, lovastatin and PD134965. . .

L7 ANSWER 555 OF 963 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:159268 BIOSIS
DOCUMENT NUMBER: PREV200100159268
TITLE: Homocysteine and **lipid lowering** agents. A comparison between **atorvastatin** and fenofibrate in patients with mixed **hyperlipidemia**.
AUTHOR(S): Giral, Philippe (1); Bruckert, Eric; Jacob, Nelly; Chapman, M. John; Foglietti, Marie-Jose; Turpin, Gerard
CORPORATE SOURCE: (1) Service d'Endocrinologie-Metabolisme, Centre de Detection et de Prevention de l'Athenosclerose, Groupe Hospitalier Pitie, Salpetriere, 47-83 Boulevard de l'hopital, 75651, Paris Cedex, 13: philippe.giral@psl.ap-hop-paris.fr France
SOURCE: Atherosclerosis, (1 February, 2001) Vol. 154, No. 2, pp. 421-427. print.
ISSN: 0021-9150.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
TI Homocysteine and **lipid lowering** agents. A comparison between **atorvastatin** and fenofibrate in patients with mixed

hyperlipidemia.

AB Background: Hyperhomocysteinemia is a risk factor for cardiovascular disease. Elevation in homocysteine levels has recently been demonstrated during **lipid lowering** treatment with fibrates. We compared the effect of a statin and a fibrate (**atorvastatin** and fenofibrate) on plasma levels of homocysteine and other thiol compounds in **hyperlipidemic** patients. Method and results: The study was of open randomized, parallel design with a preliminary screening phase, and a 6 week placebo period. After the placebo period, patients were allocated randomly to **atorvastatin** or fenofibrate for a 6 month period. Plasma thiols were assayed by high pressure liquid chromatography with fluorescence detection. There were 29 patients in the fenofibrate group and 24 in the **atorvastatin** group. Fenofibrate induced a significant increase in both homocysteine and cysteine plasma levels (+35.8 and +18%, respectively, $P < 0.0001$); by contrast, cysteinylglycine remained stable. There were no significant changes in any thiol compounds in the **atorvastatin** group. Both treatments induced a significant decrease in uric acid, although fenofibrate was noticeably more effective than **atorvastatin** (-22.8 and -6.4%, respectively). Fenofibrate induced a non-significant increase in creatinine (12%) while **atorvastatin** reduced it (4.7%, NS). Conclusion: Our study confirms that the induction of elevations in plasma homocysteine and cysteine levels are. . .

L7 ANSWER 545 OF 963 MEDLINE
ACCESSION NUMBER: 96404219 MEDLINE
DOCUMENT NUMBER: 96404219
TITLE: Plasma mevalonic acid, an index of cholesterol synthesis in vivo, and responsiveness to HMG-CoA reductase inhibitors in familial hypercholesterolaemia.
AUTHOR: Naoumova R P; Marais A D; Mountney J; Firth J C; Rendell N B; Taylor G W; Thompson G R
CORPORATE SOURCE: MRC Lipoprotein Team and Department of Clinical Pharmacology, Hammersmith Hospital, London, UK.
SOURCE: ATHEROSCLEROSIS, (1996 Jan 26) 119 (2) 203-13.
Journal code: 95X. ISSN: 0021-9150.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
AB . . . familial hypercholesterolaemia (FH) of whom 7 were treated with pravastatin 10-40 mg/day, 7 with simvastatin 10-40 mg/day and 21 with **atorvastatin** 80 mg/day. Reductions in low density lipoprotein (LDL) cholesterol and MVA on maximal dose therapy differed significantly between the three drugs: 34.7%, 42.9% and 54.0% (P = 0.0001), and 31.6%, 48.9% and 58.8% (P = 0.004), respectively. Patients on **atorvastatin** were subdivided according to whether their **reduction** in LDL **cholesterol** on treatment was above or below the mean percentage change for the whole group. Basal values of LDL cholesterol did. . . a higher basal level of plasma MVA, i.e. a higher rate of cholesterol synthesis, which was more susceptible to pharmacological **inhibition**. The more marked **cholesterol lowering** effect of **atorvastatin** 80 mg/day presumably reflects, at least in part, its ability to inhibit HMG-CoA reductase to a greater extent than maximal. . .

L7 ANSWER 546 OF 963 MEDLINE
ACCESSION NUMBER: 96267408 MEDLINE
DOCUMENT NUMBER: 96267408
TITLE: Effect of age and gender on pharmacokinetics of atorvastatin in humans.
AUTHOR: Gibson D M; Bron N J; Richens A; Hounslow N J; Sedman A J; Whitfield L R
CORPORATE SOURCE: Department of Pharmacokinetics/Drug Metabolism, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105, USA.
SOURCE: JOURNAL OF CLINICAL PHARMACOLOGY, (1996 Mar) 36 (3) 242-6.
Journal code: HT9. ISSN: 0091-2700.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
AB **Atorvastatin** is a new 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) **reductase inhibitor** that **reduces** plasma **cholesterol** by **inhibiting cholesterol**

AB OBJECTIVE--To assess the **lipid-lowering** effect of **atorvastatin** (a new 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitor) on levels of serum triglycerides and other lipoprotein fractions in patients with primary hypertriglyceridemia, determine if **atorvastatin** causes a redistribution of triglycerides in various lipoprotein fractions, and assess its safety by reporting adverse events and clinical laboratory. . . level of 6.80 mmol/L (603.3 mg/dL) and a mean baseline low-density lipoprotein cholesterol (LDL-C) level of 3.07 mmol/L (118.7 mg/dL). INTERVENTIONS--**Cholesterol-lowering** diet (National Institutes of Health National Cholesterol Education Program Step I Diet) and either 5 mg, 20 mg, or 80 mg of **atorvastatin**, or placebo. MAIN OUTCOME MEASURES--Percent change from baseline in total triglycerides for three dose levels of **atorvastatin** compared with placebo. RESULTS--Mean reductions in total triglycerides between 5 mg, 20 mg, and 80 mg of **atorvastatin** and placebo after 4 weeks of treatment were -26.5%, -32.4%, -45.8%, and -8.9%, respectively. Mean reductions in LDL-C were -16.7%,. . . changes in LDL triglycerides (-22.5%, -30.7%, -39.9%, and +3.9%) and VLDL triglycerides (-28.1%, -34.0%, -47.3%, and -10.8%) were seen. CONCLUSIONS--In **atorvastatin** treatment groups, total serum triglyceride levels decreased in a dose-dependent manner, reductions in the 20-mg and 80-mg groups were statistically significant ($P < .05$) compared with placebo. **Atorvastatin** did not cause a redistribution of triglycerides but consistently lowered triglycerides in all lipoprotein fractions. **Atorvastatin** was well tolerated.

synthesis and increasing cellular uptake of low density lipoproteins. The effects of age and gender on the pharmacokinetics of **atorvastatin** after administration of single 20-mg tablets of **atorvastatin** were studied in 16 young and 16 elderly volunteers (8 men and 8 women in each age group). Plasma equivalent concentrations of **atorvastatin** were quantitated by a validated enzyme inhibition bioassay. **Atorvastatin** was well tolerated by the participants. The equivalent maximum concentration (Cmax) of **atorvastatin** was 42.5% higher in elderly participants (age, 66-92 years) than in young participants (age, 19-35 years) and 17.6% higher in. . . respectively, in women than in men. Because the primary site of action for HMG-CoA reductase inhibitors is the liver and **atorvastatin** is subject to extensive first-pass hepatic metabolism, it is unclear whether these age- and gender-related differences in the pharmacokinetics of **atorvastatin** will be clinically important. Results of subsequent safety and efficacy trials should help clarify the clinical significance of these pharmacokinetic. . .

L7 ANSWER 547 OF 963 MEDLINE
ACCESSION NUMBER: 96240432 MEDLINE
DOCUMENT NUMBER: 96240432
TITLE: Levels of soluble cell adhesion molecules in patients with dyslipidemia.
AUTHOR: Hackman A; Abe Y; Insull W Jr; Pownall H; Smith L; Dunn K; Gotto A M Jr; Ballantyne C M
CORPORATE SOURCE: Department of Medicine, Baylor College of Medicine, Houston, Tex., USA.
CONTRACT NUMBER: HL-42550 (NHLBI)
SOURCE: CIRCULATION, (1996 Apr 1) 93 (7) 1334-8.
Journal code: DAW. ISSN: 0009-7322.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
AB . . . patients (74 +/- 9 ng/mL) compared with control subjects (48 +/- 5 ng/mL). Ten hypercholesterolemic patients were treated aggressively with **atorvastatin** alone or a combination of colestipol and either **atorvastatin** or simvastatin for a mean of 42 weeks and had an average LDL **cholesterol reduction** of 51%. Comparison of soluble CAMs before and after treatment showed a significant reduction only in sE-selectin (77 +/- 11 versus 56 +/- 6 ng/mL, P < or = .03) but not for sVCAM-1 or sICAM-1. CONCLUSIONS: Although severe **hyperlipidemia** is associated with increased levels of soluble CAMs, aggressive **lipid-lowering** treatment had only limited effects on the levels. Increased levels of soluble CAMs in patients with **hyperlipidemia** may be a marker for atherosclerosis.

L7 ANSWER 548 OF 963 MEDLINE
ACCESSION NUMBER: 96143535 MEDLINE
DOCUMENT NUMBER: 96143535
TITLE: Effect of food on the bioavailability of atorvastatin, an HMG-CoA reductase inhibitor.
AUTHOR: Radulovic L L; Cilla D D; Posvar E L; Sedman A J; Whitfield L R

CORPORATE SOURCE: Department of Pharmacokinetics/Drug Metabolism, Parke-Davis
Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105, USA.
SOURCE: JOURNAL OF CLINICAL PHARMACOLOGY, (1995 Oct) 35 (10) 990-4.
Journal code: HT9. ISSN: 0091-2700.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605

AB To determine whether **atorvastatin**, a new HMG-CoA reductase inhibitor, could be administered with food in Phase II and III clinical trials, a nonblind, randomized, two-way crossover study was conducted to assess the effect of food on rate and extent of **atorvastatin** absorption. Sixteen healthy volunteers received single 80-mg **atorvastatin** capsule doses on two occasions one week apart: once after an 8-hour overnight fast and once with a medium-fat breakfast. The single 80-mg **atorvastatin** capsule doses were well-tolerated. Mean maximum plasma **atorvastatin** equivalent concentration (Cmax) and area under the concentration-time curve (AUC) values with food were 47.9% and 12.7% lower, respectively, than. . . 32.0 hours, respectively, with food and 2.6 and 35.7 hours, respectively, without food. A medium-fat breakfast decreased the rate of **atorvastatin** absorption significantly, but had little impact on extent of drug absorption. Changes in rate of **atorvastatin** absorption are not expected to have a clinically significant effect, as subsequent multiple-dose clinical studies have shown that dose but not plasma **atorvastatin** concentration profiles correlates with **lipid -lowering** effects.

L7 ANSWER 549 OF 963 MEDLINE
ACCESSION NUMBER: 96134955 MEDLINE
DOCUMENT NUMBER: 96134955
TITLE: Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia.
AUTHOR: Bakker-Arkema R G; Davidson M H; Goldstein R J; Davignon J;
Isaacsohn J L; Weiss S R; Keilson L M; Brown W V; Miller V T; Shurzinske L J; Black D M
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co, Ann Arbor, Mich 48105-1047, USA.
SOURCE: JAMA, (1996 Jan 10) 275 (2) 128-33.
Journal code: KFR. ISSN: 0098-7484.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199604

103

L6 ANSWER 20 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 2000038721 PCTFULL EW 200027 ED 20000721
TITLE (ENGLISH): COMBINATIONS OF CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS AND
NICOTINIC ACID DERIVATIVES FOR CARDIOVASCULAR INDICATIONS
TITLE (FRENCH): COMBINAISONS D'INHIBITEURS DE LA PROTEINE DE TRANSFERT
DU
CHOLESTERYLE-ESTER ET DE DERIVES DE L'ACIDE NICOTINIQUE UTILISEES DANS
LE CADRE DE TROUBLES CARDIO-VASCULAIRES
INVENTOR(S): SIKORSKI, James, A.; GLENN, Kevin, C.
PATENT ASSIGNEE(S): G.D. SEARLE & CO.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000038721	A1	20000706

DESIGNATED STATES: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 1999-US27942	19991217
PRIORITY (ORIGINAL):	US 1998-60/113955	19981223
	US 1999-60/142684	19990707

ABEN The present invention provides combinations of cardiovascular therapeutic compounds for the prophylaxis or treatment of cardiovascular disease including hypercholesterolemia, atherosclerosis, or **hyperlipidemia**. Combinations disclosed include a nicotinic acid derivative combined with a cholesteryl ester transfer protein (CETP) inhibitor.

DETD . . . diseases, and specifically relates to combinations of compounds, compositions, and methods for their use in medicine, particularly in the prophylaxis and treatment of **hyperlipidemic** conditions such as are associated with atherosclerosis, hypercholesterolemia, and other coronary artery disease in mammals. More particularly, the invention relates to cholesteryl ester transfer. . .

It is well-settled that **hyperlipidemic** conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis.. . .

Buch et al. (PCT Patent Application No. WO 9911263) describe a combination therapy comprising **amlodipine** and a statin compound for treating subjects suffering from

angina pectoris, atherosclerosis, combined **hypertension** and **hyperlipidemia**, and to treat symptoms of cardiac arrest. Buch et al. describe in PCT Patent Application No. WO 9911259 a combination therapy comprising **amlodipine** and **atorvastatin**.

Scott et al. (PCT Patent Application No. WO 9911260) describe a combination therapy comprising **atorvastatin** and an antihypertensive agent.

. . .

of a first amount of an CETP inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of **hyperlipidemia**, atherosclerosis, or hypercholesterolemia, wherein said first and second amounts together comprise an anti-**hyperlipidemic** condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of the compounds. For example one of. . .

. . .

the instant invention comprises the use of any of the cardiovascular combination therapies described herein for the prophylaxis or treatment of hypercholesterolemia, atherosclerosis, or **hyperlipidemia**. Therefore, in one embodiment the present invention provides a method for the prophylaxis or treatment of a **hyperlipidemic** condition comprising administering to a patient in need thereof a combination in unit dosage form wherein the combination comprises a first amount of. . . acid derivative compound and a second amount of a CETP inhibiting compound wherein the first amount and the second amount together comprise an anti-**hyperlipidemic** condition effective amount of the compounds.

"Combination therapy" means the administration of two or more therapeutic agents to treat a **hyperlipidemic** condition, for example atherosclerosis and hypercholesterolemia. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a. . . therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the **hyperlipidemic** condition.

. . .

to qualify the combined amount of inhibitors in the combination therapy. This combined amount will achieve the goal of reducing or eliminating the **hyperlipidemic** condition.

"Therapeutic compound" means a compound useful in the prophylaxis or treatment of a **hyperlipidemic** condition, including atherosclerosis and hypercholesterolemia.

Dosages, Fo=ulations, and Routes of Administration
The compositions of the present invention can be administered for the prophylaxis and treatment of **hyperlipidemic** diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of action in the body,. . .

Treatment Regimen
The dosage regimen to prevent, give relief from, or ameliorate a disease condition having **hyperlipidemia** as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or blood levels with the. . .

Initial treatment of a patient suffering from a **hyperlipidemic** condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the **hyperlipidemic** disease condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for. . . which together exhibit satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the **hyperlipidemic** condition.

. . .
the combination therapy
disclosed herein may be reduction of the amount of any individual therapeutic compound, or all therapeutic compounds, effective in treating **hyperlipidemic** conditions such as atherosclerosis and hypercholesterolemia.

. . .
a first amount of an CETP inhibitor and a second amount of another cardiovascular therapeutic useful in the prophylaxis or treatment of **hyperlipidemia**, atherosclerosis, or hypercholesterolemia wherein said first and second amounts together comprise an anti-**hyperlipidemic** condition effective amount, an anti-atherosclerotic condition effective amount, or an anti-hypercholesterolemic condition effective amount of said compounds. For example one of. . .

. . .
the instant invention
comprises the use of any of the cardiovascular combination therapies described herein for the prophylaxis or treatment of hypercholesterolemia, atherosclerosis, or **hyperlipidemia**.

. .

L6 ANSWER 24 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011259 PCTFULL
TITLE (ENGLISH): THERAPEUTIC COMBINATIONS COMPRISING AMLODIPIN AND **ATORVASTATIN**
TITLE (FRENCH): COMBINAISONS THERAPEUTIQUES COMPRENANT DE L' **AMLODIPINE** ET DE L'ATORVASTATINE
INVENTOR(S): BUCH, Jan; SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S): PFIZER INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9911259	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-IB1225 19980811
PRIORITY (ORIGINAL): US 1997-60/057275 19970829

102(d)

=> d ibib kwic 20-24

L6 ANSWER 20 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 2000038721 PCTFULL EW 200027 ED 20000721
TITLE (ENGLISH): COMBINATIONS OF CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS AND NICOTINIC ACID DERIVATIVES FOR CARDIOVASCULAR INDICATIONS
TITLE (FRENCH): COMBINAISONS D'INHIBITEURS DE LA PROTEINE DE TRANSFERT DU CHOLESTERYLE-ESTER ET DE DERIVES DE L'ACIDE NICOTINIQUE UTILISEES DANS LE CADRE DE TROUBLES CARDIO-VASCULAIRES
INVENTOR(S): SIKORSKI, James, A.; GLENN, Kevin, C.
PATENT ASSIGNEE(S): G.D. SEARLE & CO.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

L6 ANSWER 22 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011263 PCTFULL
TITLE (ENGLISH): COMBINATION THERAPY COMPRISING **AMLODIPINE** AND A STATIN COMPOUND
TITLE (FRENCH): THERAPIE COMBINEE COMPRENANT DE L'**AMLODIPINE** ET UN COMPOSE DE STATINE
INVENTOR(S): BUCH, Jan; SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S): PFIZER PRODUCTS INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9911263	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-IB1220 19980810
PRIORITY (ORIGINAL): US 1997-60/057555 19970829

L6 ANSWER 23 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011260 PCTFULL
TITLE (ENGLISH): COMBINATION THERAPY COMPRISING **ATORVASTATIN** AND AN ANTIHYPERTENSIVE AGENT
TITLE (FRENCH): THERAPIE COMBINEE UTILISANT DE L'ATORVASTATINE ET UN ANTIHYPERTENSEUR
INVENTOR(S): SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S): PFIZER INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9911260	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-IB1230 19980811
PRIORITY (ORIGINAL): US 1997-60/057276 19970829

L6 ANSWER 24 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011259 PCTFULL
TITLE (ENGLISH): THERAPEUTIC COMBINATIONS COMPRISING AMLODIPIN AND **ATORVASTATIN**
TITLE (FRENCH): COMBINAISONS THERAPEUTIQUES COMPRENANT DE L'**AMLODIPINE** ET DE

	L'ATORVASTATINE
INVENTOR(S):	BUCH, Jan; SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S):	PFIZER INC.
LANGUAGE OF PUBL.:	English
LANGUAGE OF FILING:	English
DOCUMENT TYPE:	Patent
PATENT INFORMATION:	

NUMBER	KIND	DATE
WO 9911259	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 1998-IB1225	19980811
PRIORITY (ORIGINAL):	US 1997-60/057275	19970829

L6 ANSWER 22 OF 24 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999011263 PCTFULL
TITLE (ENGLISH): COMBINATION THERAPY COMPRISING **AMLODIPINE** AND A STATIN COMPOUND
TITLE (FRENCH): THERAPIE COMBINEE COMPRENANT DE L'**AMLODIPINE** ET UN COMPOSE DE STATINE
INVENTOR(S): BUCH, Jan; SCOTT, Robert, Andrew, Donald
PATENT ASSIGNEE(S): PFIZER PRODUCTS INC.
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9911263	A1	19990311

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1998-IB1220 19980810
PRIORITY (ORIGINAL): US 1997-60/057555 19970829
TIEN COMBINATION THERAPY COMPRISING **AMLODIPINE** AND A STATIN COMPOUND
TIFR THERAPIE COMBINEE COMPRENANT DE L'**AMLODIPINE** ET UN COMPOSE DE STATINE
ABEN This invention relates to pharmaceutical combinations of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and statins or pharmaceutically acceptable salts thereof, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined **hypertension** and **hyperlipidemia** and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and statins or pharmaceutically acceptable salt thereof whereby those additive and synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined **hypertension** and **hyperlipidemia** and those subjects presenting with symptoms of cardiac risk, including humans.

ABFR Cette invention se rapporte des combinaisons pharmaceutiques d'**amlodipine** ou d'un sel d'addition d'acide de celle-ci acceptable sur le plan pharmaceutique et de statines ou de sels de celles-ci acceptables sur. . . contenant ces combinaisons et des proc d s d'utilisation de ces combinaisons pour traiter des sujets souffrant d'angine de poitrine, d'ath roscl rose, d'**hypertension** et d'hyperlipid mie combin es et pour traiter des sujets pr sentant des sympt mes de risques cardiaques, notamment chez l'homme. Cette invention se rapporte des combinaisons additives et synergiques d'**amlodipine** ou d'un sel d'addition d'acide de celle-ci, acceptable sur

le plan pharmaceutique, et de statines ou de sels de celles-ci acceptables sur le plan pharmaceutique, ces combinaisons additives et synergiques servant traiter des sujets souffrant d'angine de poitrine, d'ath roscl rose, d'**hypertension** et d'hyperlipid mie combin es et des sujets pr sentant des sympt mes de risques cardiaques, y compris chez l'homme.

DETD COMBINATION THERAPY COMPRISING **AMLODIPINE** AND A STATIN COMPOUND

This invention relates to pharmaceutical combinations of **amlodipine** or pharmaceutically acceptable acid addition safts thereof and statins and pharmaceutically acceptable salts thereof, kits containing such combinations and methods of using such combinations to treat subjects suffering from angina pectoris, atherosclerosis, combined **hypertension** and **hyperlipidemia** and to treat subjects presenting with symptoms of cardiac risk, including humans. This invention also relates to additive and synergistic combinations of **amlodipine** or a pharmaceutically acceptable acid addition saft and statins; or pharmaceutically acceptable safts thereof whereby those additive and synergistic combinations are useful in treating subjects suffering from angina pectoris, atherosclerosis, combined **hypertension** and **hyperlipidemia** and those subjects presenting with symptoms or signs of cardiac risk, including humans. -

BACKGROUND OF THE INVENTION

The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA). . . . . which is incorporated herein by reference; dalvastatin, disclosed in European Patent Application Publication No. 738510 A2A, fluindostatin, disclosed in European Patent Application Publication No. 363934 Al; **atorvastatin**, disclosed in U.S. Patent No. 4,681,893, which is incorporated herein by reference; **atorvastatin** calcium, disclosed in U.S. Patent No. 5,273,995, which is incorporated herein by reference; and dihydrocompacfin, disclosed in U.S. 4,450,171, which is incorporated herein by. . .

Amlodipine and related dihydropyridine compounds are disclosed in U.S. . . . 4,572,909, which is incorporated herein by reference, as

potent anti-
ischemic and antihypertensive agents. U.S. Patent No.4,879,303, which
is
incorporated herein by reference, discloses **amlodipine**
benzenesulfonate
saft (also
termed **amlodipine besylate**). Arnlodipine and
amlodipine besylate are
potent and
long lasting calcium channel blockers. As such, **amlodipine,**
arnlodipine
besylate and
other pharmaceutically acceptable acid addition salts of
amlodipine have
utility as
antihypertensive agents and as antischemic agents. **Amlodipine**
and its
pharmaceutically acceptable acid addition salts are also disclosed in U.
S. Patent No.
5,155,120 as having utility in the treatment of congestive heart
failure.

Amlodipine
besylate is currently sold as Norvasc!9. **Amlodipine**
has the formula
H
I
CH 3 N CH 2 OCH 2 CH2 NIH 2
CHP C02 CH 2 CH 3
0 Cl

Amlodipine helps to prevent myocardial ischemia in patients
with
exertional
angina pectoris by reducing Total Peripheral Resistance, or afterload,
which reduces
the rate pressure product. . .

Further, **amlodipine** has been shown to increase myocardial
oxygen supply
by dilating
the coronary arteries.

Hypertension frequently coexists with hypedipidemia and both
are
considered
to be major risk factors for developing cardiac disease ultimately
resulting in adverse
cardiac events. This clustering of risk factors is potentially due to a
common
mechanism. Further, patient compliance with the management of
hypertension is
generally better than liatient compliance with **hyperlipidemia.**
It would
therefore be
advantageous for patients to have a single therapy which treats both of
these
conditions.

. . .

the presence of diabetes and the sex of the subject. Incidence is also affected by smoking and left ventricular hypertrophy which is secondary to **hypertension**. To meaningfully reduce the risk of coronary heart disease, R is important to manage the entire risk spectrum. For example, **hypertension** intervention trials have failed to demonstrate full normalization in cardiovascular mortality due to coronary heart disease. Treatment with cholesterol synthesis inhibitors in patients with. . .

Kramsch et al., Journal of Human **Hypertension** (1995) (Suppl. 1), 53-59 discloses the use of calcium channel blockers, including **amlodipine**, to treat atherosclerosis. That reference fu ' rther suggests that atherosclerosis can be treated with a combination of **amlodipine** and a lipid lowering agent. Human tdals have shown that calcium channel blockers have beneficial effects in the treatment of eariy atherosclerotic lesions. (see,. . . the effect of a calcium channel blocker on the progression of coronary atherosclerosis, Circulation, 1990, 82, 1940-53.) U.S. 4,681,893 discloses that certain statins, including **atorvastatin**, are hypolipidernic agents and as such are useful in treating atherosclerosis. Jukema et al., Circulation, 1995 (Suppl. 1), 1-197 disclose that there is. . . with lipid lowedng agents (e.g., HMG-CoA reductase inhibitors), specifically pravastatin. Orekhov et al., Cardiovascular Drugs and Therapy, 1997, 11, 350 disclose the use of **amlodipine** in combination with lovastatin for the treatment of atherosclerosis.

SUMMARY OF THE INVEN-nON

This invention is directed to a pharmaceuctical composition, hereinafter termed *Composition A7, comprising an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof, an amount of a statin or a pharmaceutically acceptable salt thereot and a pharmaceutically acceptable carrier, provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

This invention is still more parliculady directed to a pharmaceutical composition of Composition AB comprising **amlodipine**

besylate.

This invention is also directed to a first pharmaceutical composition, hereinafter termed gComposition B", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from **hypertension** and **hyperlipidemia**, which effects are greater than the sum of the antihypertensive and hypolipidernic effects achieved by administering said first and second pharmaceutical compositions separately and which second. . . an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said stafin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

This invention is more particularly directed to a composition of Composition BA wherein said second composition comprises **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed "C", for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from **hypertension** and **hyperlipidemia**, which effects are greater than the sum of the antihypertensive and hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and. . . of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carder or diluent said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or dilluent, provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

This invention is still more particularly directed to a composition of Composition CA comprising **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed wComposition D', for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidernic effect in a

mammal suffering from **hypertension** and **hyperlipidemia**
, which effects are
greater
than the anfihypertensive and hypolipidernic effects achieved by
administering said
first or second pharmaceutical compositions separately and which second
pharmaceutical composition. . . of a statin or a
pharmaceutically
acceptable salt thereof and a pharmaceutically acceptable carrier or
diluent, said first
pharmaceutical composition comprising an amount of **amlodipine**
or a
pharmaceutically acceptable acid addition salt thereof and a
pharmaceutically
acceptable carrier or diluent; provided that said statin is not
atorvastatin or a
pharmaceutically acceptable salt thereof.

This invention is still more particularly directed to a composition of
Composition D comprising **amlodipine besylate**.

This invention is also directed to a first pharmaceutical composition,
hereinafter termed gComposition E", for use with a second
pharmaceutical
composition for achieving a artfihypertensive effect and a hypolipidemic
effect in a
mammal suffering from **hypertension** and **hyperlipidemia**
, which effects are
greater
than the antihypertensive and hypolipidemic effects achieved by
administering said
first or second pharmaceutical compositions separately and which second
pharmaceutical composition comprises an amount of **amlodipine** or
a
pharmaceutically acceptable acid addition salt thereof and a
pharmaceutically
acceptable carrier or diluent, said first pharmaceutical composition
comprising an
amount of a statin or a pharmaceutically acceptable salt thereof and a
pharmaceutically acceptable carrier or diluent; provided that said
statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

. . .
amount of a statin
or a
pharmaceutically acceptable salt thereof and a pharmaceutically
acceptable carrier or
diluent, said first pharmaceutical composition comprising an amount of
amlodipine or
a pharmaceutically acceptable acid addition salt thereof and a
pharmaceutically
acceptable carder or dilluent; provided that said statin is not
atorvastatin or a
pharmaceutically acceptable salt thereof.

This invention is more particularly directed to a composition of
Composition
FA comprising **amlodipine besylate**.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition GR, for use with a second pharmaceutical composition for achieving. . . the sum of the antiangina effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

This invention is more particularly directed to a composition of Composition GA wherein said second pharmaceutical composition comprises **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition Hw, for use with a second pharmaceutical composition for achieving. . . of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutically acceptable acid adcrition salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

This invention is sfill more particularly directed to a pharmaceutical composition of Composition H comprising **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition J", fbr use wfth a second pharmaceutical composition for achieving. . . greater than the antianginal effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an

amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

. . .

sum of the antiatherosclerotic effects achieved by administering said first and second pharmaceutical composiflons separately and which second pharmaceutical composition comprises an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of a statin or a pharmaceutically acceptable salt thereof and. a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt thereof.

This invention is more particulady directed to a composition, hereinafter termed "Composition KB", of Composition KA wherein said second pharmaceutical composition comprises **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed 'Composition U, for use with a second pharmaceutical composition for. . . of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceLtdcally acceptable salt thereof.

This invention is more particularly directed to a composition, hereinafter termed "Composition LBO, of Composition LA comprising **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition Mn, for use with a second pharmaceutical composition for achieving. . . of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a

pharmaceutically
acceptable salt
thereof.

This invention is still more particularly directed to a composition of
cjaim M
comprising **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition,
hereinafter termed "Composition N", for use with a second
pharmaceutical
composition for achieving. . . is
greater than the antiatheroscleotic effects achieved by administering
said first or
second pharmaceutical compositions separately and which second
pharmaceutical
composition comprises an amount of **amlodipine** or a
pharmaceutically
acceptable
acid addition salt thereof and a pharmaceutically acceptable carrier or
diluent, said
first pharmaceutical composition comprising an amount of a statin or a
pharmaceutically acceptable salt thereof and a pharmaceutically
acceptable carrier or
diluent; provided that said statin is not **atorvastatin** or a
pharmaceutically acceptable
salt thereof.

. . .
an
amount of a
statin or a pharmaceutically acceptable salt thereof and a
pharmaceutically
acceptable carrier or dfluent, said first pharmaceutical composition
comprising an
amount of **amlodipine** or a pharmaceutically acceptable acid
addition salt
thereof and
a pharmaceutically acceptable carrier or diluent, provided that said
statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

This, invention is more particularly directed to a composition of
Composition
PA comprising **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition,
hereinafter termed 'Composition Q' for use with a second pharmaceutical
composition for. . . the sum of the cardiac.risk
management
effects achieved by administering said first and second pharmaceutical
compositions
separately and which second pharmaceutical composition comprises an
amount of
amlodipine or a pharmaceutically acceptable acid addition salt
thereof
and a
pharmaceutically acceptable carrier or diluent, said first
pharmaceutical composition

comprising an amount of a statin or a pharmaceutically acceptable salt thereof and a
pharmaceutically acceptable carrier or dilluent, provided that said statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

This invention is more particularly directed to a composition of Composition
QA wherein said second phannaceutical composition comprises **amlodipine**
besylate.

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composibon R", for use with a second pharmaceutical composition for. . . an
amount of a
statin or a pharmaceutically acceptable salt thereof and a pharmaceutically
acceptable cpMer or diluent, said first pharmaceutical composition comprising an
amount of **amlodipine** or a pharmaceutically acceptable acid addition salt
thereof and
a pharmaceutically acceptable carrier or diluent; provided that said statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

This invention is still more particularly directed to a composition of Composition R comprising **amlodipine besylate.**

This invention is also directed to a first pharmaceutical composition, hereinafter termed "Composition Sm, for use with a second pharmaceutical
composition for managing. . . greater than the cardiac risk management
effects
achieved by administering said first or second pharmaceutical compositions
separately and which second pharmaceutical composition comprises an amount of
amlodipine or a pharmaceutically acceptable acid addition salt thereof
and a
pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition
comprising an amount of a statin or a pharmaceutically acceptable salt thereof and a
pharmaceutically acceptable carrier or diluent; provided that said statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

a. an amount of **amlodipine** or a pharmaceutically acceptable
acid addition salt thereof and a pharmaceutically acceptable carrier or diluent in a first
unit dosage form;
b. an amount. . . in a second
unit dosage
form; and

C. container means for containing said first and second dosage forms; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable
salt thereof.

This invention is more particularly directed to a kit, hereinafter "Kit AZ", of lot
AA comprising **amlodipine besylate**.

This invention is also particularly directed to a kit of Kit A wherein said
therapeutic effect is treatment of **hypertension** and
hypedipidemia.

. . .

This invention is also directed to a kit, hereinafter termed OKit AE", of " AZ
wherein said therapeutic effect is treatment of **hypertension**
and
hyperlipidemia.

. . .

for
treating a mammal in need of therapeutic treatment comprising administering to said
mammal
(a) an amount of a first compound, said first compound being
amlodipine or a pharmaceutically acceptable acid addition salt thereof;
and
(b) an amount of a second compound, said second compound being
statin or a. . . and s aid second compound are each
optionally and
independently administered together with a pharmaceutically acceptable carrier or
diluent;
provided that said statin is not **atorvastatin** or a
pharmaceutically
acceptable salt
thereof.

This invention is more particularly directed to a method, hereinafter termed
"Method AB', of Method AA comprising **amlodipine**
besylate.

This invention is also particularly directed to a method of Method AF wherein
said thempeutic treatment comprises arib'**hypertensive** treatment
and
antihyperlipidemic treatment.

. . .

S ena ntiomers; may be prepared as
described by
Arrowsmith et al., J. Med. Chem., JM 2,% 1696. The calcium channel blocking
activfty of **amlodipine** is substantially confined to the S(-)
isomer and
to the racemic
mbcture containing the R(+) and S(-) forms. (see International Patent

Application
Number PCT/EP94/02697).. . .

amlodipine or a pharmaceutically acceptable acid addition salt thereof
and a statin or
a pharmaceutically acceptable salt thereof. The combination of this invention may
also hdude a pharmaceutically acceptable carrier or diluent
Amlodipine is a potent calcium channel blocker and as such has utility
in the
treatment of **hypertension**. **Amlodipine** is prepared as described in U.S.
Patent No.
4,57Z909, which is incorporated herein by reference. **Amlodipine besylate,**
which is
currently sold as Norvase, may be prepared as described in U.S. Patent No.
4,879,303, which is incorporated herein by reference. **Amlodipine**
,
amlodipine
besylate and other pharmaceutically acceptable acid addition safts of
amlodipine are
potent and long lasting calcium channel blockers. Other acid addition safts of
amlodipine may be prepared by reacting the free base form of **amlodipine**
with the
appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the
hydrobromide, the p-toluenesuffonate, the acetate), the hydrogen form.

. the hydrogen phosphate or the phosphate are
desired,
the appropriate and exact chemical equivalents of acid will generally be used. The
free base of **amlodipine** and the acid are usually combined in a co-
solvent from which
the desired salt precipitates, or can be otherwise is lated. . .
. . .
saft of sirrivastatin, pravastatin,
rivastatin, mevastatin,
fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin ,
lovastatin or pharmaceutically acceptable salts thereof. However, it is to be noted
that **atorvastatin** or a pharTnaceuticaly acceptable saft thereof is not
within the scope
of this disclosure.

In addition, **amlodipine** and pharmaceuficaDy acceptable acid addition
salts

thereof may occur as hydrates or solvates. Further, the statins of the instant
invention and the pharmaceutically acceptable. . .
. . .
are all
adapted to therapeutic use as agents in the treatment of atherosclerosis,
angina
pectoris, and a condition characterized by the presence of both **hypertension** and
hypedipidemia in mammals, particularly humans. Further, since these diseases and
conditions are cAosely related to the development of cardiac disease and adverse
cardiac conditions,. . .
. . .
saft thereof
and a statin
on the progression/regression of coronary and carotid artery disease. The study is
used to show that a combination of **amlodipine** or a pharmaceutically
acceptable acid
addition saft and a statin is effective in slowing or arresting tie progression or causing
regression of existing coronary. . .
. . .
of carotid arterial compliance at
designated testM
centers. This establishes baselines; for each subject. Once admitted into the test,
subjects are randomized to receive **amlodipine besylate**
(10 mgs) and
placebo or a
statin (dose is dependent upon the particular statin used, however generally 80 mgs
will be used at first) and placebo or **amlodipine**
besylate (10 mgs) and a
statin (80
rngs). It will be recognized by a skilled person that the free base form or other saft
forms of **amlodipine besylate** or the free base forrn
or other saft forms
of the statin
may be used in this invention. Calculation of the dosage amount for these other
forms of the statinand **amlodipine besylate** is easily
accomplished by
performing a
simple ratio relative to the molecular weights of the species involved. The amount of
amlodipine may be varied as required. Generally, a subject will start
out taking 10 mg
and the amount will be fitrated down to. . .

The primary objective of this study is to show that the combination of
amlodipine or a pharmaceutically acceptable acid addition salt

and a
statin reduces
the progression of atherosclerotic lesions as measured by quantitative
Coronary
angiography (QCA) in. . .
. . .
of all
segment
averages is determined to arrive at the average mean segment diameter.
The mean
segment diameter of subjects taking a statin and **amlodipine** or
a
pharmaceutically
acceptable acid addition saft will decline more slowly, will be halted
completely, or
there will be an increase in the mean. . .

The secondary objective of this study is that the combination of
amlodipine or
a pharmaceutically acceptable acid addition saft and a statin reduces
the rate of
progression of atherosclerosis in the carotid arteries as measured. .

slope of the
maximum intimal-medial thickness measurements averaged over 12 separate
wall
segments (Mean Max) as a function of time, more than does
amlodipine or
a
pharmaceutically acceptable acid addition saft or a statin alone. The
intimal-medial
thickness of subjects taking a statin and **amlodipine** or a
pharmaceutically acceptable
saft thereof will increase more slowly, will cease to increase or w91
decrease. These
results represent slowed progression of atherosclerosis,. . .

Effect of **Amlodipine** and a Statin. Ajone
and in Combination. on the
Treatment of Angina
This study is a double blind, parallel arm, randomized study to show
the
effectiveness of **amlodipine** or a pharmaceutically acceptable
acid
addition saft
thereof and a statin given in combination in the treatment of
symptomatic angina.
. . .
one of OV following four arms of the study- (1) placebo; (2) a statin
(about 2.5 mg
to about 160 mg); (3) **amlodipine** besylaWabout 2.5 mg to about
20 mg); or
(4) a
combination of the above doses of amkxfipine besylate and a statin
togeftr. The
subjects. . . to twenty four weeks. It will be
recognized by a
skilled person that the free base form or other saft forms of

amlodipine
besylate or the
free base form or other saft fbrms of the statin may be used in this invention.

Calculation of the dosage amount for these other forms of the statinand **amlodipine**
besylate is easily accomplished by performing a simple ratio relative to
the molecular
weights of the species involved.

The utility of the compounds of the present invention as medical agents in the
treatment of **hypertension** and **hyperlipidemia** in
mammals (e.g., humans)
suffering
from a combination of **hypertension** and **hyperlipidemia**
is demonstrated by
the
activity of the compounds of this invention in conventional assays and the clinical
protocol described below.

Effect of **Amlodipine** and a Statin.Alone and in
Combination, on the Treatment of Su .jects Having
Both Eb=rtension and HyMdipidemia
Thisstudy is a double blind, parallel. . . study to show the effectiveness of amlocripine or a pharmaceutically acceptable acid addition saft
thereof and a statin given in combination in controlling both **hypertension** and
hyperlipidernia in subjects who have mild, moderate, or severe **hypertension** and
hyperlipidemia.

Entry criteria: Subiects are male or female adults between 18 and 80 years of
age having both hypedipidernia and **hypertension**. The presence of
hypedipidemia is
evidenced by evaluation of the low density lipoprotein (LDL) level of the subject
relative to certain positive risk factors.. . . If the subject has no coronary heart disease
(CHD) and has less than two positive risk factors, then the subject is considered to
have **hyperlipidemia** which requires drug therapy if the LDL of the
subject is greater
than or equal to 190. If the subject has no CHD and has two or more positive risk
factors, then the subject is considered to have **hyperlipidemia** which
requires drug
therapy if the LIDL of the subject is greater than or equal to 160. If the subject has
CHID, then the. . .

. . .
the subject is a current smoker,
(5) the subject
has diabetes, (6) an HIDL of less than 45, and (7) the subject has
hypertension. An
HDL of greater than 60 is considered a negative risk factor and will
offset one of the
above mentioned positive risk factors.

The presence of **hypertension** is evidenced by a sitting
diastolic blood
pressure (BP) of greater than 90 or sitting systofic, BP of greater than
140. All. . .

After the baseline investigations are performed subjects are started on
one of
the following: (1) a fixed dose of **amlodipine besylate**
, generally about
2.5 to 10 mg;
(2) a fixed dose of a statin, generally about 2.5 mg to about 160 mg; or
(3) a
combination of the above doses of **amlodipine besylate**
and a statin
together. It will be
recognized by a skilled person that the free base form or other saft
forms of
amlodipine besylate or the free base form or other
saft forms of the
statin may be
used in this invention. Calculation of the dosage amount for these other
forms of the
statinand **amlodipine besylate** is easily accomplished
by performing a
simple ratio
relative to #* molecular weights of the species involved. Subjects
remain on these
doses for a. . .
. . .
an
adverse cardiac event is demonstrated by the acW4 of the compounds of
this
invention inconventional assays and the clinical protocol described
below-
Effects of **Amlodipine** and a Stafin. Alone
and In Combination. on Subjects at Risk
of Future Cardiovascular Events
This study is a double blind, parallel arm,. . . above the mean as
calculated by the Framiingham Risk Equation.
The
study is used to evaluate the efficacy of a fixed combi-tation of
amlodipine or a
pharmaceutically acceptable acid addition saft and a statin in
controlling
cardiovascular risk by controlling both **hypertension** and
hyperfipidemia
in patients
who have both mild to moderate **hypertension** and
hyperlipidemia.

After the baseline investigations are performed patients will be started on one of the following: (1) a fixed dose of **amlodipine besylate** (about 2.5 to 10 mg); (2) a fixed dose of a statin (about 2.5 mg to about 160 mg); or (3) the combination of the above doses of **amlodipine besylate** and a statin. Patients are kept on these doses and are asked to return in six to eight weeks so that the. . .

The above assays demonstrating the effectiveness of amodipine or pharmaceutically acceptable acid addition salts thereof and **atorvastatin** or pharmaceutically acceptable salts thereof in the treabrient of angina pectods, atherosclerosis, **hypertension** and **hyperlipidemia** together, and the management of cardiac risK also provide a means whereby the activities of the compounds of this invention can be compared between. . .

In general, in accordance with this invention, **amlodipine** is generally administered in a dosage of about 2.5 mg to about 20 mg. Preferably, **amlodipine** is administered in a dosage of about 5 mg to about 10 mg. It will be recognized by a skilled person that the free base form or other saft forms of **amlodipine besylate** may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other saft forms of **amlodipine besylate** is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

amlodipine or a pharmaceutically acceptable acid addition saft thereof and a statin or a pharmaceuticaly acceptable saft thereof. The Idt includes container means for containing. . .

CLM a. an amount of **amlodipine** or a pharmaceutically acceptable acid addition saft thereof;
b. an amount of a statin or a pharmaceutically acceptable saft thereof-, and
c. a pharmaceutically acceptable carrier or diluent;
provided that said statin is not **atorvastatin** or a

pharmaceutically
acceptable saft
thereof.

4. A pharmaceutical composition of claim 3 comprising **amlodipine besylate.**

5. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal suffering from **hypertension** and hypedipidemia, which effects are greater than the sum of the antihypertensive and hypoUpidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of **amlodipine** or a pharmaceutically acceptable acid addition saft thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of a statin or a pharmaceutically acceptable saft thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof.

7. A composition of claim 6 wherein said second pharmaceutical composition comprises **amlodipine besylate.**

8. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a antihypertensive, effect and a hyporipidemic effect in a mammal suffering from **hypertension** and **hyperlipidemia,** which effects are greater than the sum of the anthypertensive and hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second. . . an amount of amlodpine, or a pharmaceutically acceptable acid addition saft thereof and a pharmaceutically acceptable carrier or diluent, provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof

9. A composition of claim 8 wherein said statin is simvastatin, Pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin. . .

10. A composition of claim 9 comprising **amlodipine besylate.**

11. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a antihypertensive effect and a hypolipidemic effect in a mammal sufferiM from **hypertension** and **hyperliPidemia**, which effects are greater than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises. . . of a statin or a pharmaceutically acceptable saft thereof and a pharmaceuticafly acceptable carrier or diluent said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutically acceptable acid addition saft thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof.

12. A composition of claim 11 comprising **amlodipine, besylate.**

13. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a antihypertermive effect and a hypolipidemic effect in a mammal sufferkV from **hypertension** and hypedipidemia, which effects are greater than the antihypertensive and hypolipidemic effects achieved by administering said first or second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of **amlodipine** or a pharmaceutically acceptable acid addition saft thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of a statin or a pharmaceutically acceptable saft thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof.

. . .
of a statin or a pharmaceutically acceptable saft thereof and a phan-naceuticalty acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaoeuticaffy acceptable acid addition saft thereof and a pharmaceutically acceptable carrier or diluent; provided that said

statin is not
atorvastatin or a pharrnaceutically acceptable saft thereof.

17. A composition of claim 16 comprising **amlodipine** besyiate.

. . .
the sum of the
antiangina effects
achieved by administering said first and second pharmaceutical compositions
separately and which second pharmaceutical composition comprises an amount of
WO 99/11263
amlodipine, or a pharmaceutically acceptable acid addition salt thereof
and a
pharmaceutically acceptable carrier or diluent said W pharmaceutical composition
comprising an amount of a statin or a pharmaceuticafly acceptable salt thereof and a
pharmaceutically acceptable carrier or diluent; provided that said statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

20. A composition of claim 19 wherein said second pharmaceutical composition comprises **amlodipine besylate.**

21. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antianginal effect in a mammal suffering
from angina. . . of a statin or a
pharmaceutically acceptable saft thereof and a pharmaceutically acceptable carrier or
diluent said first pharmaceutical composition cornpfising an amount of
amlodipine or a
pharmaceutically acceptable acid addition salt thereof and a, pharmaceutically
acceptable carrier or diluent; provided that said statin is not
atorvastatin or a
pharmaceutically acceptable salt thereof.

. . .
greater &w the antianginal effects
achieved by
administering said first or second pharmaceutical compositions separately and which
second pharmaceutical composition comprises an amount of
amlodipine or
a
pharmaceuticafty acceptable acid addition salt t1vueof and a pharmaceutically
acceptable carrier or diluent said first pharmaceutical composition comprising an
amount of a statin or a pharmaceuticaly acceptable salt thereof and a
pharmaceuticilly acceptable carrier or diluent; provided that said statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

. . .
sum of the antiatherosclerotic effects
achieved by

administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of **amlodipine** or a pharmaceutically acceptable acid addition saft thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of a statin or a pharmaceutically acceptable saft thereof and a pharmaceutically acceptable carrier. or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof.

. . .

of simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin or lovastatin-

27. A composition of claim 26 wherein said second pharmaceutical composition comprises **amlodipine besylate.**

. . .

of a statin or a pharmaceutically acceptable saft thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutallly acceptable acid addifim saft thereof and a pharmaceutically acoeptabi e carTier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof.

38. A composition of claim 37 comprising **amlodipine besylate.**

47. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antatherosderobc effect in a mammal, which effect is. . . of a statin or a pharmaceutically acceptable saft thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of **amlodipine** or a pharmaceutically acceptable acid addition saft ftreof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable saft thereof.

48. A composition of claim 47 comprising **amlodipine besylate.**

49. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving an antiatherosclerotic effect in a mammal, which effect is. . . greater than the antiatheroscleotic effects

achieved by
administering
said first or second pharmaceutical compositions separately and which
second
pharmaceutical composition comprises an amount of **amlodipine** or
a
pharmaceutically
acceptable acid addition saft thereof and a pharmaceutically acceptable
carrier or
diluent, said first pharmaceutical composition comprising an amount of a
statin or a
pharmaceutically acceptable saft U*reof and a pharmaceutically
acceptable carrier or
diluent; provided that said statin is not **atorvastatin** or a
pharmaceutically acceptable
saft thereof.

. . .

ai statin or a pharmaceuficagy acceptable saft #Weof and a
pharmaceutically acceptable carrier or diluent said first pharmaceutical
composition
comprising an amount of **amlodipine** or a phaffnaceuficaffy
acceptable
acid addition
saft thereof and a phannaceutically acceptable carrier or diluent,
provided that said
statin is not **atorvastatin** or a pharmaceutically acceptable
saft thereof.

. . .

sum of the
cardiac risk
management effects achieved by administering said first and second
pharmaceutical
compositions separately and which second pharmaceutical composition
comprises an
amount of **amlodipine** or a pharmaceutically acceptable acid
addition saft
thereof and a
pharmaceutically acceptable carrier or diluent, said first
pharmaceutical composition
comprising an amount of a statin or a pharmaceuticafly acceptable saft
thereof and a
pharmaceutically acceptable carrier or diluent, provided that said
statin is not
atorvastatin or a pharmaceutically acceptable saft thereof.

56. A composition of claim 55 wherein said second pharmaceutical composition comprises **amlodipine besylate**.

57. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of. . . an
amount of a
statin or a pharmaceutically acceptable saft thereof and a
pharmaceutically acceptable
carrier or dii6ent, said first pharmaceutical composition comprising an
amount of
amlodipine or a pharmaceutically acceptable acid addition saft
thereof

and a
pharmaceutically acceptable carrier or dfluent; provided that said statin is not
atorvastatin or a pharmaceutically acceptable saft thereof.

58. A composition of claim 57 comprising **amlodipine besylate.**

59. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of. . . greater than the cardiac risk management
effects achieved by administering said first or second pharmaceutical compositions
separately and which second pharmaceutical composition comprises an amount of
amlodipine or a pharmaceuticafty acceptable acid addition salt thereof
and a
pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition
comprising an amount of a statin or a pharmaceutically acceptable salt thereof and a
pharmaceutically acceptable carrier or diluent; provided that said statin is not
atorvastatin or a pharmaceutically acceptable salt thereof.

a. an amount of **amlodipine** or a pharmaceutically acceptable acid
addition salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit
dosage form;
b. an amount. . . in a second unit dosage
form; and
C. container means for containing said first and second dosage forms; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable salt
thereof.

62. A kit of claim 61 comprising **amlodipine besylate.**

63. A method for treating a mammal in need of therapeutic treatment comprising administering to said mammal
(a) an amount of a first compound, said first compound being
amlodipine or a pharmaceutically acceptable acid addition salt thereof-,
and
(b) an amount of a second compound, said second compound being statin or a. . . and said second compound are each optionally and
independently administered togedw with a pharmaceutically acceptable carrier or
diluent; provided that said statin is not **atorvastatin** or a pharmaceutically acceptable
saft thereof.

65. A method of claim 64 comprising **amlodipine,**

besylate.